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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,718	12/14/2001	Karl H. Weisgraber	UCAL-222	5282

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,718	WEISGRABER ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7,14 and 20-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,14 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Response, filed 8/9/05, has been entered. Claims 1, 5, 7, 14, 20-22, are pending and under current examination.

Claim Objections

Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim recites that the cell of claim 5 is homozygous for the modified apoE allele. However, Applicants' amendment, filed 8/9/05, limits the disruption in the mouse to a homozygous disruption (see claim 1). Thus, the limitation that the cell is homozygous for the disrupted allele fails to limit the parent claim.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c). For the Oath/Declaration filed 8/21/02, the middle intial of Karl Weisgraber has been changed, but not initialed or dated. The residence, mailing address and of Li-Ming Dong has been changed, but neither initialed nor dated.

Response to Arguments

Applicants' arguments, regarding the rejection of claims 1, 3, 5, 7, 14, 15 and 20-22, under 112, 1st paragraph, for enablement (see the prior Office action, mailed 5/17/05), are found to be persuasive in view of application's amendment to the claims, reciting a homozygous mouse. This rejection is withdrawn.

New Matter

The amendment filed **7/6/04** is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment adds Figures 5A and 5B, which introduce new matter into the instant disclosure with regard to the human apoE4 sequence (SEQ ID NO: 1) and the alignment of sequences from various other species (SEQ ID NO: 2-13).

See also *Ex parte* Raible 8 USPQ2d 1709, which requires that "an incorporating statement clearly identify the subject matter which is incorporated and where it is to be found," *In re* de Seversky, MPEP §608.01(p).

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. 37 CFR 1.57(f). In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). See also MPEP §608.01 (p). Applicants

are advised that a filing of an appropriate declaration or affidavit accompanying this amendment would overcome this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 7, 14, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification teaches that human apoE4 exhibits domain interaction due to the presence of an Arg-112, together with an Arg-61, and a Glu-255, and that mouse apoE contains the *equivalent* of Arg-112 and Glu-255, but lacks the critical Arg-61 required for domain interaction. Instead, the mouse apoE contains a Thr-61. See p. 3, ¶ 0009. The claimed invention is directed to mice, cells and methods of using the mice wherein a modified endogenous apoE polypeptide comprises a

Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4. The specification fails to provide adequate written description for a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4, as claimed, to indicate that Applicants had possession of the claimed invention.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification, and which are not conventional in the art as of Applicants' effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the invention as a whole) such that one of skill in the art would recognize the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of a Thr→Arg substitution at a position equivalent to amino acid 61 of human apoE4 lacks a written description. The specification fails to describe what position(s) in an endogenous mouse apoE4 protein would be considered equivalent to the amino acid 61 of the human apoE4. Applicants are advised, as noted above, that the filing of an appropriate affidavit or declaration, accompanying the incorporation by reference of the alignment of the ApoE4 gene would overcome this rejection.

The skilled artisan could not envision such equivalent positions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolation. See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to

be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Enablement

Claims 1, 5, 7, 14, 20-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The claimed transgenic mice, cells isolated from the mice, and methods of utilizing the mice in methods of identifying agents are not enabled because the specification fails to provide teachings or guidance with regard to the particular human sequence with amino acid 61 which would be used to identify the amino acid equivalent in the mouse sequence. The specification teaches the generation of a non-human gene-targeted animal for the study of apolipoprotein E4 [apoE4] pathologies, wherein the endogenous apoE of the gene targeted animal is genetically altered such that the encoded recombinant apoE polypeptide exhibits domain interaction. It is this domain interaction that is representative of human apoE4 domain, and as such, these animals can be used as models for human apoE4 domain interaction. In particular, the specification teaches a gene-targeted mouse comprising a modified mouse apoE4 gene, wherein the modification comprises a Thr→Arg substitution at a position equivalent to the amino acid 61 of human apoE4. See p. 6, ¶ 0020.

MPEP §608.01 (p) states that:

> *A disclosure in an application, to be complete, must contain such description and details as to enable any person skilled in the art or science to which the invention pertains to make and use the invention as of its filing date. In re Glass, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974). While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention.*

The specification is not enabling for the instant invention because it fails to teach the particular sequence that would be used such that one of skill in the art would be able to identify the amino acid substitution equivalent to amino acid 61 in human apoE4. Note that the identification of amino acid number 61 in the human apoE4 would be relative to the sequence used. After careful review of the specification, the Examiner is unable to identify the particular human sequence that would be used (by SEQ ID NO., for example) in the methods as claimed, such that one of skill in the art would be able to identify both amino acid 61 of the human apoE4 and a position equivalent to that amino acid in the mouse apoE4 gene. The human amino acid sequence of apoE4 is considered essential subject matter and has been improperly incorporated by reference (Weisgraber (1994), *Adv. Protein Chem.*) [see p. 3, ¶ 0009 of the specification] (See Applicants' amendment, filed 7/6/04). An appropriate declaration or affidavit accompanying the above-identified amendment, would overcome this rejection.

Accordingly, in view of the quantity of experimentation necessary for the production and use of mice comprising a homozygous modification of the endogenous apoE allele, wherein the modified allele encodes a modified apoE polypeptide that exhibits domain interaction characteristic of human apoE4 and the modified polypeptide comprises a Thr→Arg substitution at a position equivalent to amino acid 61 of the human apoE4, the lack of teaching or guidance provided by the specification with regard to the human apoE4 sequence, it would have required

undue experimentation for one of skill in the art to make and/or use the claimed non-human animals and methods of using the same.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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